REMARKS UNDER 37 CFR § 1.111

Formal Matters

Claims 1-8, 10-12, 15 and 16 are pending after entry of the amendments set forth herein.

Claims 1-8, 10-12 and 15 were examined. Claims 1-8, 10-12 and 15 were rejected. Claim 15 was withdrawn.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

No new matter has been added.

The Office Action

In the Official Action of January 6, 2006, the Examiner withdrew claim 16 as being drawn to a method that is distinct from that presented in the original claims. Accordingly, the Examiner withdrew claim 16 from consideration as being directed to a non-elected invention.

Objection to the Specification

The Examiner objected to the disclosure as containing an embedded hyperlink at page 35, line 8. In response thereto, Applicants have amended the specification above to remove the embedded hyperlink on page 35, line 8 of the specification. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the objection to the disclosure as being no longer appropriate.

Claim Rejected Under 35 U.S.C. Section 112, First Paragraph

Claim 10 was rejected under 35 U.S.C. Section 112, first paragraph as failing to comply with the written description requirement, the Examiner asserting that there is no adequate description in the specification of the limitation "each normalized signal intensity being functionally related to a mole fraction of sample molecules that hybridize to the respective feature". Although Applicants do not agree with this ground of rejection, and respectfully submit that it would be readily apparent to one of ordinary

skill in the art that this limitation is supported in the specification, such as at pages 23-25, for example, and thus, Applicants do not acquiesce to this ground of rejection, Applicants have nevertheless amended the rejected phrase in claim 10 above to recite: each normalized signal intensity being directly mathematically related to a mole fraction of sample molecules that hybridize to the respective feature and inversely mathematically related to a mole fraction of sample molecules that hybridize to the calibration feature. It is respectfully submitted that support for the amended recitation is provided in the specification at page 23, line 13 – page 24, line 25.

In view of the above amendment and remarks, the Examiner is respectfully requested to reconsider the rejection of claim under 35 U.S.C. Section 112, first paragraph as failing to comply with the written description requirement, as being inappropriate.

Claim Rejected Under 35 U.S.C. Section 112, Second Paragraph

Claim 10 was rejected under 35 U.S.C. Section 112, second paragraph as being indefinite. The Examiner asserted that metes and bounds of the phrase "each normalized signal intensity being functionally related to a mole fraction of sample molecules that hybridize to the respective feature" are unclear because the meaning of the phrase "functionally related" is vague in the context of the claim. The Examiner further stated that it was unclear what is meant by having a signal intensity functionally related to a fraction of molecules in a sample, as it was unclear how the signal intensity can relate to the function of the molecules. In response thereto, Applicants note that the rejected language referred to the signal intensity being mathematically functionally related to the mole fraction of molecules, To further clarify this meaning, Applicants have amended the rejected phrase in claim 10 above to recite: each normalized signal intensity being directly mathematically related to a mole fraction of sample molecules that hybridize to the respective feature and inversely mathematically related to a mole fraction of sample molecules that hybridize to the calibration feature. It is respectfully submitted that support for the amended recitation is provided in the specification at page 23, line 13 – page 24, line 25.

In view of the above amendment and remarks, the Examiner is respectfully requested to reconsider the rejection of claim under 35 U.S.C. Section 112, second paragraph as being indefinite, as being inappropriate.

Claims Rejected Under 35 U.S.C. Section 102(b) (Lockhart et al.)

Claims 1, 7-8 and 15 were rejected under 35 U.S.C. Section 102(b) as being anticipated by Lockhart et al., WO 97/10365. The Examiner asserted that Lockhart et al. uses an array containing control probes that include normalization controls, expression level controls and mismatch controls. The Examiner asserted that in one embodiment, Lockhart et al. discloses that the difference between signal intensities of a perfect match (PM) probe and a mismatch (MM) probe for each pair of PM and MM are calculated, and then the average of the differences for all the pairs is calculated. The Examiner referred to page 61, first paragraph, and page 103, claims 66-67 as support for this assertion.

Applicants respectfully disagree with the Examiner's assertion. The text of page 61, first paragraph of Lockhart et al. reads as follows:

> "Once all the pairs of probes have been processed and the expression of the gene indicated, an average of ten times the LRs is computed at step 275. Additionally, an average of the IDIF values for the probes that incremented NPOS and NNEG is calculated. These values may be utilized for quantitative comparisons of this experiments with other experiments."

The "LRs" that Lockhart et al. refers to, and from which an average of ten times their amounts is computed, are log ratios for pairs of PM and MM probes for genes that are indicated as expressed or not expressed, see page 59, lines 13-15. Genes that are indicated as expressed or not expressed are those genes for which the difference between the signal intensities of PM and MM for that gene (i.e., I_{PM} - I_{MM}) after background subtraction, is greater than or equal to the difference threshold AND the quotient of the hybridization intensities of the pair (I_{PM} /I_{MM}) is greater than or equal to the ratio threshold, see page 58, lines 25-30. Since page 61 continues the example described on pages 58-59 and with reference to Fig. 9, it is clear that computation of "an average of ten times the LRs" disclosed on page 61, line 2 refers to the log ratios only those PM-MM pairs which, after background subtraction where I_{PM} -I_{MM} is greater than or equal to the difference threshold and where I_{PM} /I_{MM} is greater than or equal to the ratio threshold, not to all PM/MM ratios as asserted by the Examiner. As further support for Applicants' position, Fig. 9 clearly shows that LRs and IDIF are computed only for NNEGs and NPOSs, see steps 260, 264 and 266 in Fig. 9.

The Examiner interpreted all of the control probes disclosed by Lockhart et al. to be calibrating probes. Thus, the Examiner interpreted the set of calibrating probes in Lockhart to be the normalization

controls, expression level controls and mismatch controls. However, the Examiner has not identified where Lockhart et al. discloses calculating a collective calibration signal intensity from the signal intensities of the normalization controls, expression level controls and mismatch controls. In the Examiner's remarks regarding Applicant's previously submitted remarks (page 7, first full paragraph of the Office Action dated 1/6/2006), the Examiner appears to change his interpretation of what the calibration probes are in Lockhart et al. when he states: "...in Lockhart et al., the set of probes that incremented NPOS or NNEG is the set of calibrating probes because their intensities are factored in the calibration. And it is the total intensities of these probes that are calculated."

It is respectfully submitted that the recited phrase "set of calibrating features" should be interpreted to have only one scope. That is, the recitation in claim 1 that includes calculating a collective calibration signal intensity from signal intensities read from the set of calibrating features" refers to the "set of calibrating features" recited in the "selecting a molecular array" recitation. The "set of calibrating features" recited in the "selecting a molecular array" recitation requires that these calibration features each contain calibrating probes that hybridize to a majority of target molecules in sample solutions to which the molecular array is intended to be exposed. It is respectfully submitted that an MM probe does not hybridize to a majority of target molecules in sample solutions to which the molecular array is intended to be exposed. This behavior is expected on the basis of the design strategy used to pick these probes. The PM probes that form the basis of the MM probes are designed to deliver maximum specificity for their intended target gene. This means that, whenever possible, the probes have been picked to exhibit the maximum possible difference from other sequences known to be present in other expressed genes from the target organism. Generally, these differences encompass several bases, and a change to a single base (as is done to produce an MM probe) would not be expected to result in a probe that promiscuously hybridizes to multiple expressed genes in real samples. This expectation is confirmed in practice: Mismatch probe hybridization intensities are usually less than the intensities of the corresponding PM probes from which they derive, and the ratio of the PM:MM intensities is reasonably constant across different samples and target gene expression levels, indicating that most of the MM signal derives from the intended hybridization target of the PM probe. In fact, it is the relative rarity of cross-hybridization to MM probes that makes them useful, since PM-MM pairs that yield near equal signals or PM:MM ratios less than 1 are usually ignored. If such events were a frequent occurrence, the array data would disappear. It follows that NPOS and NNEG also do not hybridize to a majority of target molecules in sample solutions to which the molecular array is intended to be exposed, as these are composed of PM and MM probe pairs, and PM probes are designed to hybridize to a

specific target molecule. Therefore, it is respectfully submitted that it is improper to consider MM probes to be members of the set of calibrating features recited in claim 1.

Still further, the Examiner has not indicated how he has interpreted the recitation of : "calculating normalized signal intensities of the features containing probes that hybridize to specific target molecules, based on signal intensities read from features of the molecular array by applying to the signal intensities a normalization function that includes the calculated collective calibration signal" to be disclosed by Lockhart et al. Fig. 8 of Lockhart et al. is a flow chart showing a process for indicating the expression of a gene according to the method of Lockhart et al. Lockhart et al. receives input of hybridization intensities of pairs of PM and MM probes with a gene (step 202), compares the hybridization intensities of the PM and MM probes of each pair (step 204) and indicates the expression of the gene according to the comparison of the hybridization intensities. There is no disclosure or suggestion of calculating normalized signal intensities of the features containing probes that hybridize to specific target molecules, based on signal intensities read from features of the molecular array by applying to the signal intensities a normalization function that includes the calculated collective calibration signal.

The determination of whether a gene is expressed or not is not made based on only one pair of PM-MM probes, but rather on an analysis of many pairs of such probes, see page 58, lines 8-10. Fig. 9 shows a flowchart of a process for determining if a gene is expressed utilizing a decision matrix. At step 252, raw scan data of N pairs of perfect match and mismatch probes are inputted. Note that these pairs are all for the same gene. For each pair of PM and MM, the intensities (I_{PM} and I_{MM}) are background-subtracted (step 256) and then compared to a difference threshold (D) and a ratio threshold (R) (step 258). If the difference between the hybridization intensities (I_{PM} - I_{MM}) of a pair is greater than or equal to D and the quotient of the intensities (I_{PM}/I_{MM}) of that pair is greater than or equal to R, than the value of NPOS is incremented at step 260. NPOS indicates the number of pairs of probes which have hybridization intensities indicating that the gene (for which the probe pairs code) is likely expressed.

If the difference between the hybridization intensities (I_{MM} - I_{PM}) of a pair is greater than or equal to D and the quotient of the intensities (I_{MM}/I_{PM}) of that pair is greater than or equal to R, than the value of NNEG is incremented at step 262. For each pair that exhibits hybridization intensities either indicating the gene is expressed or not expressed a log ratio value (LR) is calculated by the log of I_{PM}/I_{MM}. IDIF is also calculated for each of these pairs as I_{PM} - I_{MM}.

A decision matrix is then used at step 272 to determine if the gene is expressed. There is no use of a calculated collective calibration signal, as recited in the present claims, for making the

determination using the decision matrix of Lockhart et al. Once all of the pairs of probes for a gene have been processed and the expression of the gene indicated, an average of ten times the LRs is computed at step 275. As noted above, these LRs are only the log ratios of those pairs of PM and MM for the same gene that have been determined to be NPOS or NNEG. These values may then be used for quantitative comparisons of the experiment from which the LRs were generated, with other experiments. There is no disclosure or suggestion of normalizing with these values.

Regarding claims 7-8, the Examiner asserted that Lockhart et al. teach that each PM signal intensity is calibrated by calculating he difference between signal intensities of the PM and its corresponding MM and that the average difference for all PM/MM is also calculated. As noted above, this is not the case, as only those pairs which qualify as NPOS or NNEG are averaged. The Examiner further concluded that, since all the differences of PM-MM are calculated similarly, they are interpreted as similar calibrating signal intensities, and that because the differences of PM-MM as a whole represent the signal intensities for all the probes on the array, they cover the entire span, i.e., overall range of signal intensities generated from the array. First, Applicants point out that not all of the differences in intensities between PM-MM pairs are calculated, as only those pairs which qualify as NPOS or NNEG are used in calculating the average. Secondly, this calculation does not represent the signal intensities for all the probes on the array, but only those probes designed for a single gene. There are many more probes (PM-MM) pairs on the array that are designed for other genes, as the array is not described as designed for a single gene.

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 1, 7-8 and 15 under 35 U.S.C. Section 102(b) as being anticipated by Lockhart et al., WO 97/10365, as being clearly inappropriate.

Claims Rejected Under 35 U.S.C. Section 103(a) (Lockhart et al. in view of Chenchik et al. and Lewin)

Claims 2-3, 5 and 10-12 were rejected under 35 U.S.C. Section 103(a) as being unpatentable over Lockhart et al., WO 97/10365 in view of Chenchik et al., U.S. Patent No. 6,077,673 and Lewin, B., (GENS IV, 1990, Oxford Press University. The Examiner applied essentially the same arguments, regarding Lockhart et al., to these claims as were applied to claims 1, 7 and 8 above. The Examiner asserted that it would be readily recognized by one of skill in the art that when the average difference is calculated, a total intensity of the difference between the PM and MM must have also been calculated,

and that, consequently, total intensities of all MM probes are also calculated. Applicants respectfully traverse these assertions, since Lockhart et al. does not calculate an average difference over all PM and MM probes, for the reasons noted above. Nor does Lockhart et al. calculate normalized signal intensities for features that are not in the set of control features based on the calculated collective calibration signal.

The Examiner asserted that Chenchik et al. teaches the use of calibration spots and control spots to provide other useful information such as background or basal level of expression, and that one of ordinary skill in the art would have been motivated to apply this teaching to search for probes that are common to the targets in the sample solution to modify Lockhart et al. to use calibrating probes that are common to the target molecules and to include poly(a) oligonucleotides on the array as extra calibrating probes. However, the Examiner did not state what such motivation would have been. Chenchik et al. merely discloses the use of orientation marks, which are useful for orienting the grid during feature extraction, and housekeeping genes and negative and positive control genes. These were all discussed in the present specification as standard types of control probes, none of which are used according to the presently claimed methods. The housekeeping genes mentioned by Chenchik et al. are used to determining basal metabolic levels and background expression levels. There is no teaching in Chenchik et al. of processing signals of the housekeeping genes in the manner that is currently recited in claims 1 and 10. Further, if these housekeeping gene probes were included in the array of Lockhart et al., there is no teaching provided as to how they would be signal processed. Negative control probes, as taught by Chenchik et al., are commonly used for background subtraction purposes, and Chenchik et al. provides no teaching as to their use for normalizing the signal intensities of the mouse gene probes. Nor does Chenchik et al. provide any teaching for using positive control probes for normalizing signal intensities of the mouse gene probes, but only indicates that they can somehow be used to provide other useful information, such as background or basal level of expression. As previously noted, Chenchik et al. does not teach or suggest a normalization procedure based on calibration probes, does not mention or suggest use of average calibration probe intensities, and does not mention use of a normalization function, and therefore is not properly combinable with Lockhart et al. to overcome the deficiencies of Lockhart et al. discussed above. Further, Lockhart et al. already discloses normalization controls and expression level controls such as probes from housekeeping genes, in addition to the mismatch controls, as noted by the Examiner. Therefore it is respectfully submitted that there would have been no motivation to add additional probes for housekeeping genes.

Nor does Lewin teach or suggest any modifications that would overcome the deficiencies of

Lockhart et al. in meeting the recitations of the present claims, since Lewin is merely a textbook reference discussing poly(a) oligonucleotides.

With regard to Applicants' previous remarks, the Examiner indicated that they were not persuasive because instant claim 1 recites calculating a collective signal intensity form the signal intensities read from the entire set of calibrating features, and, in Lockhart et al., the set of probes that incremented NPOS or NNEG is the set of calibrating probes because their intensities are factored in the calibration. In response thereto, Applicants note that claim 1 has been amended above to recited that each of the calibrating features in the set of calibrating features claimed, contains calibrating probes that hybridize to a majority of target molecules in sample solutions to which the molecular array is intended to be exposed. The PM and MM probes of Lockhart et al., whether or not they qualify as NPOS or NNEG, do not hybridize to a majority of target molecules in the sample solution applied to the array of Lockhart et al.

Regarding Chenchik et al., the Examiner stated that the significance of the teaching provided is that calibrating probes should not be unique to a particular target in the sample, but "common" to the targets. However, as noted, Chenchik et al. does not provide any teaching or method of a normalization process to be carried out with the spots described. Further, Lockhart et al. already discloses normalization controls and expression level controls such as probes from housekeeping genes, in addition to the mismatch controls, as noted by the Examiner. Therefore it is respectfully submitted that there would have been no motivation to add additional probes for housekeeping genes, and even if these references were properly combinable, which Applicants respectfully submit that they are not, Chenchik et al. would not modify the method of determining gene expression based on PM and MM probes that is described in Lockhart et al.

The Examiner further argued that the limitation of calculating normalized signal intensities for features that are not in the set of control features is not recited in the claims. Applicants respectfully disagree. Although this is not recited verbatim, claim 1 recites calculating normalized signal intensities of the features containing probe that hybridize to specific target molecules. It is respectfully submitted that features containing probe that hybridize to specific target molecules are features that are not in the set of control features.

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claims 2-3, 5, and 10-12 under 35 U.S.C. Section 103(a) as being unpatentable over Lockhart et al. (WO 97/10365) as applied to claims 1, 7-8 and 15 above, and further in view of Chenchik et al., U.S. Patent No. 6,077,673 and Lewin, B., (GENS IV, 1990, Oxford

Press University), as being inappropriate.

Claim Rejected Under 35 U.S.C. Section 103(a) (Lockhart et al. in view of Chenchik et al. and Darnell et al.)

Claim 4 was were rejected under 35 U.S.C. Section 103(a) as being unpatentable over Lockhart et al. (WO 97/10365) as applied to claims 1, 7-8 and 15 above, and further in view of Chenchik et al., U.S. Patent No. 6,077,673 and Darnell et al. (Molecular Cell Biology, Eds., 1990, published by Scientific American Books). The Examiner applied essentially the same arguments, regarding Lockhart et al., to these claims as were applied to claims 1, 7-8 and 15 above. It is respectfully submitted that this ground of rejection is inappropriate for the same reasons presented above with regard to Lockhart et al. and Chenchik et al. with regard to claims Claims 1-3, 5, 7-8, 10-12 and 15, as Darnell et al. is directed only to a description of Alu sequence and does nothing to overcome the deficiencies of Lockhart et al. and Chenchik et al. in meeting the recitations of claims 1 and 10 from which the other claims depend.

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claim 4 under 35 U.S.C. Section 103(a) as being unpatentable over Lockhart et al. (WO 97/10365) as applied to claims 1, 7-8 and 15 above, and further in view of Chenchik et al., U.S. Patent No. 6,077,673 and Darnell et al. (Molecular Cell Biology, Eds., 1990, published by Scientific American Books), as being inappropriate.

Claim Rejected Under 35 U.S.C. Section 103(a) (Lockhart et al. in view of Chenchik et al. and Feinberg et al.)

Claim 6 was rejected under 35 U.S.C. Section 103(a) as being unpatentable over Lockhart et al. (WO 97/10365) as applied to claims 1, 7-8 and 15 above, and further in view of Chenchik et al., U.S. Patent No. 6,077,673 and Feinberg et al. (Analytical Biochemistry, Vol. 132, pages 6-13, 1983). The Examiner applied essentially the same arguments, regarding Lockhart et al., to these claims as were applied to claims 1, 7-8 and 15 above. It is respectfully submitted that this ground of rejection is inappropriate for the same reasons presented above with regard to Lockhart et al. and Chenchik et al., as Feinberg et al. is directed only to a method of labeling DNA by using a mixture of random hexamer as primers. Although the Examiner states that such would have been an ideal probed for use by Chenchik et al., neither Chenchik et al. nor Feinberg et al. teaches or suggests processing an array according to the

methods presently claimed. Further, since Lockhart et al. also fails to carry out the method steps claimed for the reasons discussed above, even if these references were properly combinable in the manner suggested by the Examiner, which Applicants respectfully submit that would not be, the resultant combination would still fail to meet the recitations of the present claims, since Lockhart et al. does not calculate the average that was asserted by the Examiner.

The Examiner argued that all of the control probes disclosed by Lockhart et al. are interpreted as calibrating probes, and that they will hybridize to a fraction of the target molecules in the sample solutions to which the array is exposed fro hybridization because the products of the housekeeping genes, etc, are contained in the sample solutions. However, the Examiner above interpreted the set of calibrating probes to be only the NPOS and NNEG PM-MM probe pairs, and accordingly the two interpretations are inconsistent. Further, under either interpretation, it is respectfully submitted that the PM-MM probe pairs do not hybridize to a majority of target molecules in the sample solution of Lockhart et al, as those NPOSs and NNEGs for which an average of LRs are calculated are all for the same gene.

In view of the above amendments and remarks, the Examiner is respectfully requested to reconsider and withdraw the rejection of claim 4 under 35 U.S.C. Section 103(a) as being unpatentable over Lockhart et al. (WO 97/10365) as applied to claims 1, 7-8 and 15 above, and further in view of Chenchik et al., U.S. Patent No. 6,077,673 and Feinberg et al. (Analytical Biochemistry, Vol. 132, pages 6-13, 1983), as being inappropriate.

Conclusion

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10020405-1.

Respectfully submitted,

LAW OFFICE OF ALAN W. CANNON

Date: 3/21/2006

By: _____

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